CLAIMS

1. A pharmaceutical composition for inhibiting growth factor receptor tyrosine kinase activity comprising a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged, and a pharmaceutically acceptable carrier.

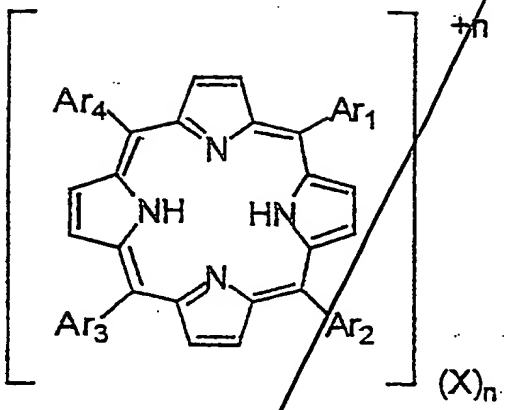
2. The pharmaceutical composition according to claim 1, wherein said growth factor receptor tyrosine kinase is selected from fibroblast growth factor (FGF) receptor tyrosine kinase, epidermal growth factor (EGF) receptor tyrosine kinase, heparin-binding EGF-like growth factor (HB-EGF) receptor tyrosine kinase, platelet derived growth factor (PDGF) receptor tyrosine kinase, vascular endothelial growth factor (VEGF) receptor tyrosine kinase, nerve growth factor (VGF) receptor tyrosine kinase, hepatocyte growth factor (HGF) receptor tyrosine kinase, insulin receptor tyrosine kinase and insulin-like growth factor (IGF) receptor tyrosine kinase.

3. The pharmaceutical composition according to claim 2 for inhibition of cell proliferation mediated by growth factor receptor tyrosine kinase activity.

4. The pharmaceutical composition according to claim 3 for: (i) inhibition of angiogenesis; (ii) inhibition of vascular smooth muscle cell proliferation in disorders including atherosclerosis, hyperthrophic heart failure and postsurgical restenosis; (iii) inhibition of cell proliferation and migration in the treatment of primary tumors and metastasis; (iv) treatment of nonmalignant tumors such as benign prostate hyperthrophy; (v) treatment of diabetic retinopathy, psoriasis, rheumatoid arthritis, and other disorders including retrolental fibroplasia, macular degeneration, hemangioma, arteriovenous malformation, hypertrophic scars, acne, scleroderma and autoimmune diseases.

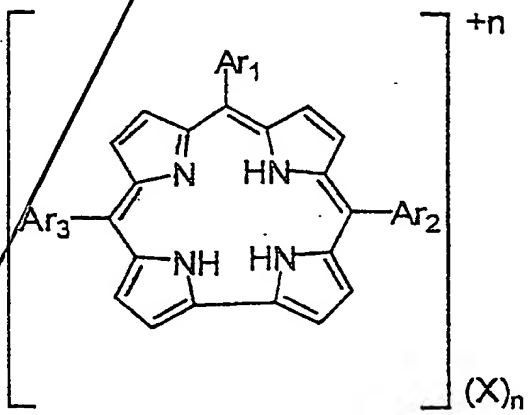
5. The pharmaceutical composition according to claim 2 for the treatment of bone and cartilage related disorders including inherited skeletal disorders, e.g. achondroplasia, dwarfism, craniosynostosis.

6. The pharmaceutical composition according to any one of claims 1-5 wherein the 5,10,15,20-tetraaryl-porphyrin has the formula:



wherein Ar_1 , Ar_2 , Ar_3 , and Ar_4 , the same or different, are each an aryl radical selected from a carboaryl, a heteroaryl and a mixed carboaryl-heteroaryl radical, at least two of said aryl radicals being positively charged, n is an integer from 2 to 4 and X is a pharmaceutically acceptable anion.

7. The pharmaceutical composition according to any one of claims 1-5 wherein the 5,10,15,20-triaryl- corrole has the formula:



wherein Ar_1 , Ar_2 , and Ar_3 , the same or different, are each an aryl radical selected from a carboaryl, a heteroaryl and a mixed carboaryl-heteroaryl radical, at least two of said aryl radicals being positively charged, n is an integer from 2 to 3 and X is a pharmaceutically acceptable anion.

8. The pharmaceutical composition according to claim 6 or 7, wherein said carboaryl radical by itself or as part of the mixed carboaryl-heteroaryl radical is a substituted monocyclic or bicyclic aromatic radical and said heteroaryl radical is a substituted 5-6 membered aromatic ring containing 1-3 heteroatoms selected from O, S and/or N.

9. The pharmaceutical composition according to claim 8, wherein said carboaryl radical is selected from phenyl, biphenyl and naphthyl substituted by one or more halogen atoms, and/or one or more C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, amino-(C_1-C_8) alkylamino, and tri-(C_1-C_8) alkylammonium radicals.

10. The pharmaceutical composition according to claim 9, wherein said carboaryl radical is phenyl substituted by fluoro and optionally by tri-(C_1-C_8) alkylammonium or amino-(C_1-C_8) alkylamino.

11. The pharmaceutical composition according to claim 10, wherein one or two of said carboaryl radicals is pentafluorophenyl and/or 4-aminopropylamino-2,3,5,6-tetrafluorophenyl.

12. The pharmaceutical composition according to claim 10, wherein one to four of said carboaryl radicals is 4-trimethylammoniophenyl or 4-trimethylammonio-2,3,5,6-tetrafluorophenyl.

13. The pharmaceutical composition according to claim 8, wherein said heteroaryl radical by itself or as part of a mixed carboaryl-heteroaryl radical is selected from furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl, triazinyl substituted by one or more halogen atoms, and/or one or more C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, amino-(C_1-C_8) alkylamino, and tri-(C_1-C_8) alkylammonium radicals.

14. The pharmaceutical composition according to claim 13, wherein said one to four of said heteroaryl radicals is N-(C_1-C_8 alkyl)-pyridylium.

15. The pharmaceutical composition according to claim 14, wherein said radical is selected from 2-, 3- or 4-(N-methyl) pyridylium.

16. The pharmaceutical composition according to claim 6 or 7, wherein said mixed carboaryl-heteroaryl radical is 4-(N-methyl-2-pyridylium)-2,3,5,6-tetrafluoro- phenyl.

17. The pharmaceutical composition according to any one of claims 1-6, wherein said porphyrin compound is selected from one of the compounds herein designated **P1, P5, P6, P7, P8, P9, P10, P15, P16, P17, P18, P19** and **P20,** namely:

P1 5,10,15,20-Tetrakis(N-methyl-4-pyridylium)-21H,23H-porphine tetra-p-tosylate

P5 5,10,15,20-Tetrakis[4-(trimethylammonio)phenyl]-21H,23H-porphine tetra-p-tosylate

P6 5,10,15,20-Tetrakis(N-methyl-4-pyridylium)-21H,23H-porphine aluminium hydroxide tetraiodide

P7 5,10,15,20-Tetrakis(N-methyl-2-pyridylium)-21H,23H-porphine tetraiodide

P8 5,10,15,20-Tetrakis(N-methyl-4-pyridylium)-21H,23H-porphine tetraiodide

P9 5,10,15,20-Tetrakis(N-methyl-2-pyridylium)-21H,23H-porphine tetra-p-tosylate

P10 3,8,13,18-Tetrakis(N-methyl-4-pyridylium)- 21H,23H-porphine tetraiodide

P15 5,10,15,20-Tetrakis(2,3,5,6-tetrafluoro-4-trimethylammonio-phenyl)-21H, 23H-methyl-porphine tetra-trifluoromethylsulfonate

P16 5-Pentafluorophenyl-10,15,20-tris(N-methyl-4-pyridylium)-21H,23H-porphine triiodide

P17 5,15-Bis(pentafluorophenyl)-10,20-bis(N-methyl-4-pyridylium)-21H,23H-porphine diiodide

P18 5,10-Bis(pentafluorophenyl)-15,20-bis(N-methyl-4-pyridylium)-21H,23H-porphine diiodide

P19 5,10,15-Tris(N-methyl-4-pyridylium)-20-(2,3,5,6-tetrafluoro-4-aminopropyl-amino-phenyl)-21H,23H-porphine triiodide

P20 5,10,15,20-Tetrakis[4-(N-methyl-2-pyridylium) 2,3,5,6-tetrafluoro-phenyl]-21H,23H-porphine tetraiodide

18. The pharmaceutical composition according to any one of claims 1-5 and 7 wherein said corrole compound is 5,10,15-Tris[2,3,5,6-tetrafluorophenyl-4-(N-methyl-2-pyridylium)]-21H,23H- corrole triiodide, herein designated **P21**.

19. The pharmaceutical composition according to claim 4 for inhibition of angiogenesis comprising the compound **P1** or **P21**.

20. The pharmaceutical composition according to claim 4 for inhibition of vascular smooth muscle cell proliferation in postsurgical restenosis comprising the compound **P1** or **P20**.

21. The pharmaceutical composition according to claim 4 for inhibition of cell proliferation and migration in the treatment of primary tumors and metastasis comprising a compound selected from the compounds **P1, P5, P7, P20** and **P21**.

22. The pharmaceutical composition according to claim 5 for inhibition of FGFR-3 tyrosine kinase activity and treatment of achondroplasia, comprising the compound **P16**.

23. Use of a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively

charged, for the preparation of a pharmaceutical composition for inhibiting growth factor receptor tyrosine kinase activity.

24. The use according to claim 23, wherein said growth factor receptor tyrosine kinase is selected from fibroblast growth factor (FGF) receptor tyrosine kinase, epidermal growth factor (EGF) receptor tyrosine kinase, platelet derived growth factor (PDGF) receptor tyrosine kinase, vascular endothelial growth factor (VEGF) receptor tyrosine kinase, nerve growth factor (VGF) receptor tyrosine kinase, hepatocyte growth factor (HGF) receptor tyrosine kinase, insulin receptor tyrosine kinase and insulin-like growth factor (IGF) receptor tyrosine kinase.

25. The use according to claim 24 for inhibition of cell proliferation mediated by growth factor receptor tyrosine kinase activity.

26. The use according to claim 25 for inhibition of angiogenesis.

27. The use according to claim 25 for inhibition of vascular smooth muscle cell proliferation in disorders including atherosclerosis, hyperthrophic heart failure and postsurgical restenosis.

28. The use according to claim 25 or 26, for inhibition of cell proliferation and migration in the treatment of primary tumors and metastasis.

29. The use according to claim 25 for treatment of nonmalignant tumors such as benign prostate hyperthrophy.

30. The use according to claim 25 for treatment of diabetic retinopathy.

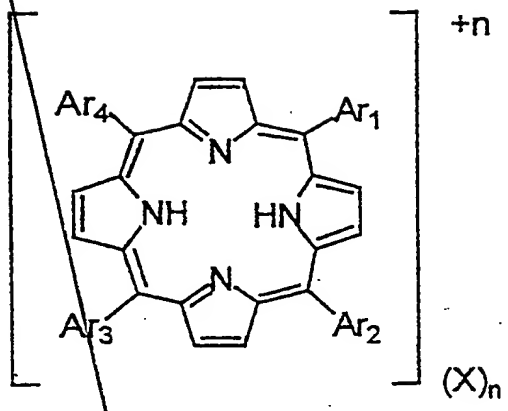
31. The use according to claim 25 for treatment of psoriasis.

32. The use according to claim 25 for treatment of rheumatoid arthritis.

33. The use according to claim 25 for treatment of disorders including retrolental fibroplasia, macular degeneration, hemangioma, arteriovenous malformation, hypertrophic scars, scleroderma and autoimmune diseases.

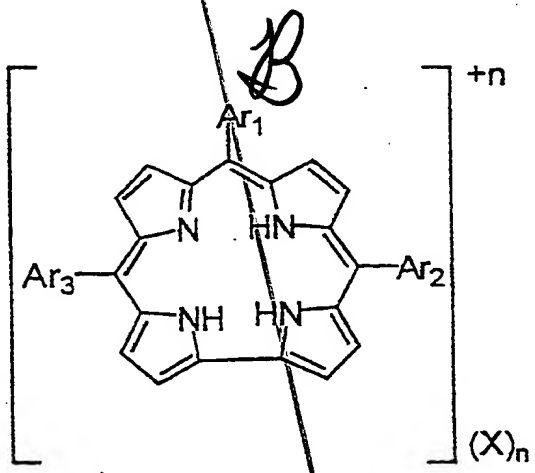
34. The use according to claim 24 for the treatment of bone and cartilage related disorders including inherited skeletal disorders e.g. achondroplasia, dwarfism, craniosynostosis.

35. The use according to any one of claims 23-34 wherein the 5,10,15,20-tetraaryl-porphyrin has the formula:



wherein Ar_1 , Ar_2 , Ar_3 , and Ar_4 , the same or different, are each an aryl radical selected from a carboaryl, a heteroaryl and a mixed carboaryl-heteroaryl radical, at least two of said aryl radicals being positively charged, n is an integer from 2 to 4 and X is a pharmaceutically acceptable anion.

36. The use according to any one of claims 23-34 wherein the 5,10,15,20-triaryl-corrole has the formula:



wherein Ar_1 , Ar_2 , and Ar_3 , the same or different, are each an aryl radical selected from a carboaryl, a heteroaryl and a mixed carboaryl-heteroaryl radical, at least two of said aryl radicals being positively charged, n is an integer from 2 to 3 and X is a pharmaceutically acceptable anion.

37. The use according to claim 35 or 36, wherein said carboaryl radical by itself or as part of the mixed carboaryl-heteroaryl radical is a substituted monocyclic or bicyclic aromatic radical and said heteroaryl radical is a substituted 5-6 membered aromatic ring containing 1-3 heteroatoms selected from O, S and/or N.

38. The use according to claim 37, wherein said carboaryl radical is selected from phenyl, biphenyl and naphthyl substituted by one or more halogen atoms, and/or one or more C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, amino-(C_1-C_8) alkylamino, and tri-(C_1-C_8) alkylammonium radicals.

39. The use according to claim 38, wherein said carboaryl radical is phenyl substituted by fluoro and optionally by tri-(C_1-C_8)alkylammonium or amino-(C_1-C_8alkyl) amino.

40. The use according to claim 39, wherein one or two of said carboaryl radicals is pentafluorophenyl and/or 4-aminopropylamino-2,3,5,6-pentafluorophenyl.

41. The use according to claim 39, wherein one to four of said carboaryl radicals is 4-trimethylammoniophenyl or 4-trimethylammonio- 2,3,5,6-pentafluorophenyl.

42. The use according to claim 37, wherein said heteroaryl radical by itself or as part of a mixed carboaryl-heteroaryl radical is selected from furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl, triazinyl substituted by one or more halogen atoms, and/or one or more C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylamino, amino-(C_1-C_8) alkylamino, and tri- (C_1-C_8) alkylammonium radicals.

43. The use according to claim 42, wherein said one to four of said heteroaryl radicals is N-(C_1-C_8alkyl)-pyridylium.

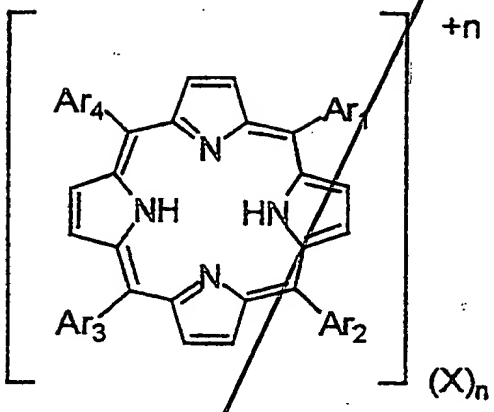
44. The use according to claim 43, wherein said radical is selected from 2-, 3- or 4-(N-methyl) pyridylium.

45. The use according to claim 35 or 36, wherein said mixed carboaryl-heteroaryl radical is 4-(N-methyl-2-pyridylium)-2,3,5,6-tetrafluoro-phenyl.

46. The use according to any one of claims 23-35, wherein said porphyrin compound is selected from one of the compounds herein designated **P1, P5, P6, P7, P8, P9, P10, P15, P16, P17, P18, P19** and **P20.**

47. The use according to any one of claims 23-34 and 36, wherein said corrole compound is the compound herein designated **P21.**

48. A 5,10,15,20-tetraaryl-porphyrin of the formula:



wherein Ar_1 , Ar_2 , Ar_3 , and Ar_4, the same or different, are each an aryl radical selected from a carboaryl, a heteroaryl and a mixed carboaryl-heteroaryl radical, at least two of said aryl radicals being positively charged, n is an integer from 2 to 4 and X is a pharmaceutically acceptable anion, and wherein at least one of the non-positively charged aryl radicals, if present, is pentafluorophenyl or 4-amino(C_1-C_8)alkylamino-2,3,5,6- tetrafluorophenyl, and at least two of the positively charged aryl radicals are N-(C_1-C_8)alkyl-pyridylium or 4-(N-C_1-C_8 alkyl-pyridylium)-2,3,5,6-tetrafluoro-phenyl.

49. The porphyrin of claim 48 being selected from one of the compounds herein designated **P16, P17, P18, P19** and **P20**.

50. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a tetrapyrrolic macrocycle selected from a 5,10,15,20-tetraaryl-porphyrin according to claim 48 and a 5,10,15-triaryl-corrole, wherein said aryl radical of the corrole compound is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged.

51. A pharmaceutical composition according to claim 50 wherein the 5,10,15,20-tetraaryl-porphyrin according to claim 48 is one of the compounds herein designated **P16, P17, P18, P19** and **P20**.

52. A pharmaceutical composition according to claim 50 wherein the 5,10,15-triaryl-corrole is a corrole as defined in any one of claims 7-16.

53. The pharmaceutical composition according to claim 52 wherein the 5,10,15-triaryl- corrole is the compound herein designated **P21**.

54. A method for inhibiting growth factor receptor tyrosine kinase activity comprising the administration of an inhibitor selected from a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged, in an amount sufficient to inhibit growth factor receptor activity.

55. A method for inhibiting angiogenesis comprising the administration of an inhibitor selected from a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged, in an amount sufficient to inhibit angiogenesis.

56. A method for prevention of restenosis after percutaneous transluminal coronary angioplasty comprising the administration of an inhibitor selected from a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged, in an amount sufficient to inhibit smooth muscle cell proliferation.

57. A method for inhibiting primary tumor growth and metastasis comprising the administration of an inhibitor selected from a tetrapyrrolic macrocycle selected from 5,10,15,20-tetraaryl-porphyrin and 5,10,15-triaryl-corrole, wherein said aryl radical is a carboaryl, a heteroaryl or a mixed carboaryl-heteroaryl radical and at least two of said aryl radicals are positively charged, in an amount sufficient to inhibit primary tumor ~~growth and metastasis.~~

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